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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
WEHBE, ANNE MARIE SABRINA	
ART UNIT	**PAPER NUMBER**
1633	

DATE MAILED: 11/01/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/869,674	WHITLEY ET AL.	
	Examiner	Art Unit	
	Anne Marie S. Wehbe	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 September 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,4,5,7-13,15-20,22,24-31 and 33* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-2,4-5,7-13,15-20,22,24-31, and 33* is/are rejected.

7)☒ Claim(s) *16* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

A request for continued examination (RCE) under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 9/1/05 has been entered. Applicant's amendment and response received currently with the RCE on 9/1/05 has also been entered. Claims 3, 6, 14, 21, 23, and 32 are canceled. Claims 1-2, 4-5, 7-13, 15-20, 22, 24-31, and 33 are currently pending and under examination in the instant application. An action on the merits follows.

Those sections of Title 35, US code, not included in this action can be found in a previous office action.

Claim Amendments

The amendment to the claims filed on 9/1/05 does not fully comply with the requirements of 37 CFR 1.121(c)(2). Claim 16 recites and "EGF-1" promoter; however, the previous version of the claims recites an "EGR-1" promoter. The current version of claim 16 does not provide markings that the applicant intended to amend the "R" to an "F" as required by 37 CFR 1.121(c)(2). However, review of the specification suggests that this is a typographical error in the

claims and not an actual amendment. As such, in the interests of compact prosecution, the amendment has been entered and claim 16 has been objected to below for minor informalities. Please note however that further amendments to the claims must comply with 37 CFR 1.121(c)(2) in order to ensure their entry.

Claim Rejections - 35 USC § 112

The rejection of previously pending claims 1-31 and 33 under 35 U.S.C. 112, first paragraph, for lack of enablement is withdrawn in view of applicant's cancellation or amendment of the claims. In particular, it is noted that the currently pending claims have been amended to recite that the recombinant HSV comprises an expressible GM-CSF encoding DNA. As such, applicant's arguments regarding the effects of GM-CSF on tumor growth are found persuasive.

Applicant's amendments to the claims have necessitated the following new grounds of rejection.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who

has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology Technical Amendments Act of 2002 do not apply when the reference is a U.S. patent resulting directly or indirectly from an international application filed before November 29, 2000. Therefore, the prior art date of the reference is determined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

Claims 1-2, 4, 17, 19-20, 24, 31, and 33 are newly rejected under 35 U.S.C. 102(e) as being anticipated by U.S. Patent No. 6,379,674 B1 (4/30/02), hereafter referred to as Rabkin et al. The applicant claims a recombinant herpes simplex virus which lacks all or part of both $\gamma_1$34.5 genes and which comprises an expressible GM-CSF encoding DNA. The applicant also claims pharmaceutical compositions comprising said recombinant HSV and methods of treating neoplastic disease comprising administering to a target tumor said recombinant HSV, wherein the target tumor is a tumor of the CNS.

Rabkin et al. teaches mutated HSV viruses which are incapable of expressing a functional $\gamma_1$34.5 gene product and which comprise at least one expressible nucleotide sequence encoding at least one immunomodulator (Rabkin et al., column 3, lines 8-15). In particular, Rabkin et al. teaches the G207 virus which is an HSV virus in which both copies of the $\gamma_1$34.5 genes contain a 1 kb deletion of the Bst EII-StuI fragment present in the $\gamma_1$34.5 genes (Rabkin et al., column 5, lines 28-41). In addition, Rabkin et al. teaches that the immunomodulator is GM-CSF (Rabkin et

al., column 8, lines 27-37). Rabkin et al. also teaches that the immunomodulator DNA is operatively linked to promoter and polyadenylation sequences (Rabkin et al., see for instance Figure 5). Rabkin et al. further teaches formulating the mutant HSV as pharmaceutical compositions and administering the compositions directly to tumors *in vivo* (Rabkin et al., columns 2-3 and 7). In particular, Rabkin et al. teaches that tumors to be targeted include tumors of the CNS, such as glioblastomas, meningiomas, Schwannomas, and astrocytomas (Rabkin et al., columns 9-10, bridging paragraph). Thus, by teaching all the elements of the claims as written, Rabkin et al. anticipates the instant invention as claimed.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 5, 19, and 22 are newly rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent No. 6,379,674 B1 (4/30/02), hereafter referred to as Rabkin et al. in view of U.S. Patent No. 5,328,688 (7/12/94), hereafter referred to as Roizman '688. The applicant claims recombinant HSV which lack all or part of both $\gamma_1$34.5 genes and which comprise an expressible GM-CSF encoding DNA wherein the $\gamma_1$34.5 genes have a stop codon at a Bst EII site in said genes, and methods of treating neoplastic disease comprising administering to a target tumor said recombinant HSV

Rabkin et al. teaches mutated HSV viruses which are incapable of expressing a functional $\gamma_1$34.5 gene product and which comprise at least one expressible nucleotide sequence encoding at least one immunomodulator (Rabkin et al., column 3, lines 8-15). In particular, Rabkin et al. teaches the G207 virus which is an HSV virus in which both copies of the $\gamma_1$34.5 genes contain a 1 kb deletion of the Bst EII-StuI fragment present in the $\gamma_1$34.5 genes (Rabkin et al., column 5, lines 28-41). Rabkin et al. also teaches that the immunomodulator is a cytokine, particularly GM-CSF (Rabkin et al., column 7, lines 50-67, and column 8, lines 27-37). Rabkin et al. further teaches formulating the mutant HSV as pharmaceutical compositions and administering the compositions directly to tumors *in vivo* (Rabkin et al., columns 2-3 and 7).

Rabkin et al. differs from the instant invention by not particularly teaching that the HSV virus which is incapable of expressing functional $\gamma_1$34.5 gene products has a stop codon at the Bst EII site in the $\gamma_1$34.5 gene. Roizman '688 supplements Rabkin et al. by teaching several different methods for making recombinant HSV which are incapable of expressing a functional

$\gamma_1$34.5 gene product. Roizman '688 teaches that the $\gamma_1$34.5 gene can be inactivated by deleting a portion of the coding sequence of the $\gamma_1$34.5 genes **or** by introducing a stop codon at a BstEII site in the $\gamma_1$34.5 gene (Roizman '688, column 2). Specifically, Roizman '688 teaches HSV R4009 in which a stop codon has been introduced at a BstEII site in both copies of the $\gamma_1$34.5 genes (Roizman '688, column 2, lines 19-23). Roizman et al. further teaches that such viruses are rendered avirulent by the inactivation of the $\gamma_1$34.5 genes (Roizman et al., column 20, claim 4). Thus, based on the motivation to make and use mutated HSV viruses which are incapable of expressing a functional $\gamma_1$34.5 gene product and which comprise at least one expressible nucleotide sequence encoding GM-CSF to treat tumors as taught by Rabkin et al., it would have been *prima facie* obvious to the skilled artisan at the time of filing to modify any of the $\gamma_1$34.5 inactivated HSV taught by Roizman '688 such as HSV R4009 in which a stop codon has been introduced at a BstEII site in both copies of the $\gamma_1$34.5 genes to include an expressible nucleotide sequence encoding GM-CSF. Based on the detailed instructions provided by Roizman '688 for making HSV R4009, and the instructions in Rabkin et al. for inserting expressible nucleotide sequences encoding a cytokine such as GM-CSF into mutant HSV, the skilled artisan would have had a reasonable expectation of success in making and using a recombinant HSV which comprises an expressible GM-CSF encoding DNA, wherein both the $\gamma_1$34.5 genes have a stop codon at a Bst EII site.

Claims 1, 7-8, 12-13, 15-16, 18-19, 25-26, and 30 are newly rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent No. 6,379,674 B1 (4/30/02), hereafter referred to

as Rabkin et al., in view of Andreansky et al. (1998) Gene Therapy, Vol. 5, 121-130. The applicant claims recombinant HSV which lack all or part of both $\gamma_1$34.5 genes and which comprise an expressible GM-CSF encoding DNA wherein both copies of the $\gamma_1$34.5 genes have been replaced by GM-CSF encoding DNA, and methods of treating neoplastic disease comprising administering to a target tumor said recombinant HSV. The applicant further claims said recombinant HSV and methods wherein the GM-CSF encoding DNA is under the promoter regulatory control of an EGR-1 herpes simplex virus promoter, and further operatively linked to a hepatitis B virus-derived polyadenylation signal.

Rabkin et al. teaches mutated HSV viruses which are incapable of expressing a functional $\gamma_1$34.5 gene product and which comprise at least one expressible nucleotide sequence encoding at least one immunomodulator (Rabkin et al., column 3, lines 8-15). In particular, Rabkin et al. teaches the G207 virus which is an HSV virus in which both copies of the $\gamma_1$34.5 genes contain a 1 kb deletion of the Bst EII-StuI fragment present in the $\gamma_1$34.5 genes (Rabkin et al., column 5, lines 28-41). In addition, Rabkin et al. teaches that the immunomodulator is GM-CSF (Rabkin et al., column 8, lines 27-37). Rabkin et al. also teaches that the immunomodulator DNA is operatively linked to promoter and polyadenylation sequences (Rabkin et al., see for instance Figure 5). Rabkin et al. further teaches formulating the mutant HSV as pharmaceutical compositions and administering the compositions directly to tumors *in vivo* (Rabkin et al., columns 2-3 and 7). In particular, Rabkin et al. teaches that tumors to be targeted include tumors of the CNS, such as glioblastomas, meningiomas, Schwannomas, and astrocytomas (Rabkin et al., columns 9-10, bridging paragraph).

While Rabkin et al. teaches using a promoter and polyadenylation sequences, Rabkin et al. differs from the instant invention by failing to teach the use of the EGR-1 promoter and HBV derived polyadenylation signal to express GM-CSF in the recombinant HSV. In addition, while Rabkin et al. teaches deleting the Bst EII-Stu I fragment of both $\gamma_1$34.5 genes, Rabkin et al. fails to specifically teach that the GM-CSF encoding DNA has been inserted into the 1 kb deletion of the Bst EII-StuI fragment. Andreansky et al. supplements Rabkin et al. by teaching a recombinant HSV-1 virus which comprises $\gamma_1$34.5 genes in which the Bst EII-StuI fragment of the $\gamma_1$34.5 genes have been replaced by IL-4 expressing DNA operatively linked to an EGR-1 promoter and HBV polyA sequence (Andreansky et al., page 122, in particular Figure 1). Andreansky et al. also teaches formulating the recombinant HSV encoding IL-4 for *in vivo* use and directly administering the virus to target tumors in the brain resulting in inhibition of tumor growth (Andreansky et al., page 125, Figure 7). While Andreansky et al. exemplifies an HSV encoding IL-4 for tumor therapy, Andreansky et al. provides motivation for using other cytokines such as GM-CSF by teaching that GM-CSF has been demonstrated to have *in vivo* tumor inhibition properties (Andreansky et al., pages 121-122, bridging paragraph). Therefore, in view of the motivation provided by Andreansky et al. for inserting a cytokine gene into the Bst EII-StuI fragment of the $\gamma_1$34.5 genes and for using the EGR-1 promoter and HBV polyA sequence as expression regulatory elements, and further in view of the teachings of Andreansky et al. that cytokines other than IL-4, such as GM-CSF, have demonstrated anti-tumor activity, it would have been *prima facie* obvious to the skilled artisan at the time of filing to replace the Bst EII-StuI fragment of the $\gamma_1$34.5 genes with GM-CSF encoding DNA in the recombinant HSV taught by Rabkin et al. and further to utilize the EGR-1 promoter and HBV polyA sequence as

expression regulatory elements to drive the expression of GM-CSF. Further, based on the substantial direction provided by Rabkin et al. and Andreansky et al. for making and modifying recombinant HSV, the high level of skill in the art of molecular and viral biology at the time filing, and the successful demonstration by both Rabkin et al. and Andreansky et al. that recombinant HSV can be used to express cytokines with known anti-tumor activity to treat tumors *in vivo*, the skilled artisan would have had a reasonable expectation of success in making recombinant HSV in which the Bst EII-StuI fragment of the $\gamma_1$34.5 genes have been replaced with GM-CSF encoding DNA operatively linked to the EGR-1 promoter and HBV derived polyadenylation sequence, and in using said recombinant HSV to treat a tumor.

Claims 1, 9-11, 19, and 27-29 are newly rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent No. 6,379,674 B1 (4/30/02), hereafter referred to as Rabkin et al., in view of U.S. Patent No. 5,641,651 (6/24/97), hereafter referred to as Roizman '651. The applicant claims recombinant HSV which lack all or part of both $\gamma_1$34.5 genes and which comprise an expressible GM-CSF encoding DNA, wherein the GM-CSF encoding DNA is under the promoter-regulatory control of a synthetic HSV-derived promoter comprising promoter sequences upstream of the transcription initiation site of the α4 gene operatively linked to the transcription initiation site and the 5' transcribed non-coding sequence of the γ_1U_L19 gene. The applicant further claims methods of treating neoplastic disease comprising administering said recombinant HSV to a target tumor.

Rabkin et al. teaches mutated HSV viruses which are incapable of expressing a functional $\gamma_1$34.5 gene product and which comprise at least one expressible nucleotide sequence encoding at

least one immunomodulator (Rabkin et al., column 3, lines 8-15). In particular, Rabkin et al. teaches the G207 virus which is an HSV virus in which both copies of the $\gamma_1$34.5 genes contain a 1 kb deletion of the Bst EII-StuI fragment present in the $\gamma_1$34.5 genes (Rabkin et al., column 5, lines 28-41). In addition, Rabkin et al. teaches that the immunomodulator is GM-CSF (Rabkin et al., column 8, lines 27-37). Rabkin et al. also teaches that the immunomodulator DNA is operatively linked to promoter and polyadenylation sequences (Rabkin et al., see for instance Figure 5). Rabkin et al. further teaches formulating the mutant HSV as pharmaceutical compositions and administering the compositions directly to tumors *in vivo* (Rabkin et al., columns 2-3 and 7). In particular, Rabkin et al. teaches that tumors to be targeted include tumors of the CNS, such as glioblastomas, meningiomas, Schwannomas, and astrocytomas (Rabkin et al., columns 9-10, bridging paragraph).

Rabkin et al. differs from the instant invention by failing to teach the use of a synthetic HSV promoter to drive cytokine expression. Roizman '651 supplements Rabkin et al. by teaching a synthetic HSV-derived promoter comprising promoter sequences upstream of the transcription initiation site of the α4 gene operatively linked to the transcription initiation site and the 5' transcribed non-coding sequence of the γ_1U_L19 gene, and the use of said promoter to drive transcription of genes in recombinant HSV (Roizman '651, column 2, and columns 11-12). Roizman '651 further provides motivation for using a synthetic HSV-derived promoter to express foreign proteins using recombinant HSV by teaching that the synthetic promoter expresses gene products throughout the infectious process of the virus and overproduces the gene product (Roizman '651, column 2, lines 16-20, and column 3, lines 7-14). Thus, based on the motivation to use the synthetic HSV promoter provided by Roizman '651 in order to express

greater amounts of proteins for a longer period of time from recombinant HSV, it would have been *prima facie* obvious to the skilled artisan at the time of filing to use the synthetic promoter described by Roizman '651 to drive expression of the GM-CSF gene in the recombinant HSV taught by Rabkin et al. Further, based on the substantial direction provided by Rabkin et al., and Roizman '651 for making and modifying recombinant HSV, and the high level of skill in the art of molecular and viral biology at the time filing, the skilled artisan would have had a reasonable expectation of success in making and using recombinant HSV which lack all or part of both $\gamma_1$34.5 genes and which comprise an expressible GM-CSF encoding DNA, wherein the GM-CSF encoding DNA is under the promoter-regulatory control of a synthetic HSV-derived promoter comprising promoter sequences upstream of the transcription initiation site of the α4 gene operatively linked to the transcription initiation site and the 5' transcribed non-coding sequence of the γ_1U_L19 gene.

Claim Objections

Claim 16 is objected to because of the following informalities: the claim appears to contain a typographical error where "EGR-1" is misspelled "EGF-1". Appropriate correction is required.

Double Patenting

Applicant is advised that should claim 12 be found allowable, claim 15 will be objected to under 37 CFR 1.75 as being a substantial duplicate thereof. Applicant is further advised that should claim 8 be found allowable, claim 16 will be objected to under 37 CFR 1.75 as being a substantial duplicate thereof. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k).

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication from the examiner should be directed to Anne Marie S. Wehbé, Ph.D., whose telephone number is (571) 272-0737. The examiner can be reached Monday- Friday from 10:30-7:00 EST. If the examiner is not available, the examiner's supervisor, Dave Nguyen, can be reached at (571) 272-0731. For all official communications, **the new technology center fax number is (571) 273-8300**. Please note that all official communications and responses sent by fax must be directed to the technology center fax number. For informal, non-official communications only, the examiner's direct fax number is (571) 273-0737. For any inquiry of a general nature, please call (571) 272-0547.

The applicant can also consult the USPTO's Patent Application Information Retrieval system (PAIR) on the internet for patent application status and history information, and for electronic images of applications. For questions or problems related to PAIR, please call the USPTO Patent Electronic Business Center (Patent EBC) toll free at 1-866-217-9197. Representatives are available daily from 6am to midnight (EST). When calling please have your application serial number or patent number available. For all other customer support, please call the USPTO call center (UCC) at 1-800-786-9199.

Dr. A.M.S. Wehbé

ANNE M. WEHBE' PH.D
PRIMARY EXAMINER